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Priority text

Biphenylcarboxylic acid amides, the preparation thereof and the use thereof as medicaments

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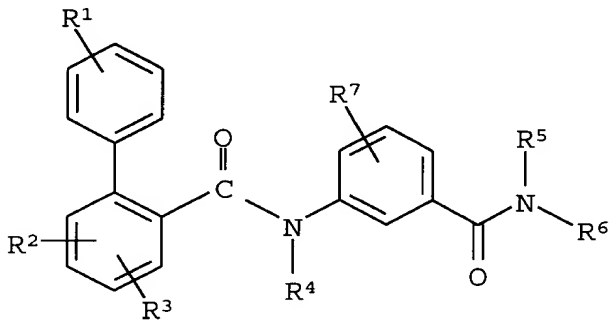
The present invention relates to biphenylcarboxylic acid amides of general formula



, (I)

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof, particularly the physiologically acceptable salts thereof which have valuable pharmacological properties, medicaments containing these compounds, their use and processes for preparing them.

The compounds of the above general formula I are valuable inhibitors of the microsomal triglyceride transfer protein (MTP) and are therefore suitable for lowering the plasma level of the atherogenic lipoproteins.

In the above general formula I

R^1, R^2 and R^3, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom, a straight-chain or branched C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino- or di-(C_{1-3}-alkyl)-amino group,

R^4 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R^5 denotes a hydrogen atom or a straight-chain or branched C_{1-6}-alkyl group and

R^6 denotes a straight-chain or branched C_{1-6}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-amino group, wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-(C_{1-3}-alkyl)-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

an arylamino, N-(C_{1-3}-alkyl)-arylamino, heteroarylamino, N-(C_{1-3}-alkyl)-heteroarylamino, C_{1-7}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-7}-alkyl-carbonylamino, arylcarbonylamino, heteroarylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino, N-(C_{1-3}-alkyl)-heteroarylcarbonylamino, C_{1-8}-alkoxy-carbonyl-amino or N-(C_{1-3}-alkyl)-(C_{1-8}-alkoxy)-carbonylamino group,

an aryl or aryl-C_{1-3}-alkyl-aryl group,

a heteroaryl group,

an aryl group substituted by a heteroaryl group,

a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-(C_{1-3}-alkyl)-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

a phenylcarbonylamino-aryl, phenylaminocarbonyl-aryl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-aryl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-aryl group,

a straight-chain or branched C_{1-6}-alkyl group which is terminally substituted

by an aryl or heteroaryl group,

by an aryl group which is fused to a heteroaryl group via two adjacent carbon atoms,

by a heteroaryl group which is fused to an aryl or heteroaryl group via two adjacent carbon atoms,

by an aryl group which is substituted by an aryl or heteroaryl group, by a 4 to 7 membered cycloalkyleneimino group, by a phenylaminosulphonyl or phenylsulphonylamino group,

by a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-8}-alkyl-carbonyl, C_{1-8}-alkoxycarbonyl, benzoyl, phenyl-(C_{1-3}-alkyl-carbonyl), C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-aryl, phenylaminocarbonyl-aryl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-aryl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-aryl group or

by a hydroxycarbonyl, C_{1-3}-alkoxycarbonyl, C_{3-7}-cycloalkyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aryl-C_{1-3}-alkoxycarbonyl or heteroaryl-C_{1-3}-alkoxycarbonyl group,

a straight-chain or branched C_{2-6}-alkyl group which is terminally substituted

by a hydroxy, C_{1-3}-alkoxy, aryloxy, heteroaryloxy-aryl-C_{1-3}-alkoxy or heteroaryl-C_{1-3}-alkoxy group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino or N-(C_{1-3}-alkyl)-heteroarylcarbonylamino group,

or R^5 and R^6 together with the enclosed nitrogen atom denote a 4- to 7-membered cycloalkyleneimino group,

R^7 denotes a hydrogen, chlorine, bromine or iodine atom, a C_{1-3}-alkyl or C_{1-3}-alkoxy group,

wherein by the term aryl group mentioned above is meant a phenyl, 1-naphthyl or 2-naphthyl group,

by the term heteroaryl group mentioned above is meant a 5-membered heteroaromatic ring linked via a nitrogen or carbon atom, which contains

an imino group, an oxygen or sulphur atom,

an imino group and an oxygen, sulphur or nitrogen atom,

an imino group and two nitrogen atoms or

two imino groups and an oxygen or sulphur atom,

or a 6-membered heteroaromatic ring linked via a carbon atom which contains one or two nitrogen atoms,

and wherein a 1,4-butadienylene group may be attached both to the abovementioned 5-membered and also to the 6-membered heteroaromatic rings in each case via two adjacent carbon atoms and the bicyclic heteroaromatic rings thus formed may also be bonded via a carbon atom of the 1,4- butadienylene group,

a hydrogen atom bonded to a nitrogen atom of the abovementioned 5-membered monocyclic or fused heteroaryl groups may be replaced by a C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl, phenylcarbonyl or phenyl-C_{1-3}-alkylcarbonyl group,

all the abovementioned phenyl, aryl and heteroaryl groups as well as aromatic or heteroaromatic parts of molecules in the carbon skeleton may be monosubstituted by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a C_{3-7}-cycloalkyl, trifluoromethyl, phenyl, hydroxy, C_{1-3}-alkoxy, trifluoromethoxy, amino, C_{1-3}-alkylamino, acetylamino, propionylamino, benzoylamino, N-(C_{1-3}-alkyl)-benzoylamino, acetyl, propionyl, benzoyl, C_{1-3}-alkoxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or cyano group or, with the exception of 5-membered heteroaryl groups or heteroaromatic parts of molecules containing more than two heteroatoms, may also be disubstituted by the abovementioned substituents, while the substituents may be identical or different,

in all the abovementioned 4- 7-membered cycloalkyleneimino groups the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms in each case may be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxycarbonyl, C_{1-6}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl or sulphonyl group or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-C_{1-3}-alkyl-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

additionally any carboxy, amino or imino group present in the abovementioned groups may be substituted by a group which can be cleaved *in vivo*, and may thus occur in the form of a prodrug group,

and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group

such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or R_eCO-O-(R_fCR_g)-O-CO group wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or R_eCO-O-(R_fCR_g)-O group wherein R_e to R_g are as hereinbefore defined,

whereby the abovementioned ester groups may also be used as a group which can be converted *in vivo* into a carboxy group.

Moreover, the saturated alkyl and alkoxy moieties which contain more than 2 carbon atoms mentioned hereinbefore and hereinafter in the definitions also include the branched isomers thereof such as, for example, the isopropyl, tert.butyl, isobutyl group, etc., unless otherwise stated.

Preferred compounds of the above general formula I are those wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom or a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms,

R^2, R^3, R^4, R^5 and R^7, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group,

R^6 denotes a straight-chain or branched C_{1-4}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-amino group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, C_{1-8}-alkoxy-carbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-aminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

a phenylamino, 1-naphthylamino or 2-naphthylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group,

a C_{1-4}-alkyl-carbonylamino, phenylcarbonylamino or C_{1-8}-alkoxy-carbonylamino group,

a phenyl, biphenyl, 1-naphthyl, 2-naphthyl or phenyl-C_{1-3}-alkylphenyl group which may be substituted in the aromatic moieties in each case by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a trifluoromethyl, hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, acetylamino, benzoylamino, acetyl, propionyl, benzoyl, C_{1-3}-alkoxy-carbonyl, amino-carbonyl, C_{1-3}-alkylamino-carbonyl or cyano group,

a heteroaryl group or a heteroaryl-phenyl group,

a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl,

phenylaminocarbonyl- or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group,

a straight-chain C_{1-3}-alkyl group which is terminally substituted

by a phenyl, biphenyl, 1-naphthyl or 2-naphthyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, a straight-chain or branched C_{1-4}-alkyl group, a trifluoromethyl, hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, acetylamino, benzoylamino, acetyl, propionyl, benzoyl, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or cyano group,

by a heteroaryl group optionally substituted in the carbon skeleton by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl or C_{1-3}-alkoxy group, by a trifluoromethyl, phenyl or cyano group,

by an indolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl or quinazolinyl group bonded via a carbon atom or, in the case of the first two groups, via a nitrogen atom,

by a phenyl group which is substituted by a heteroaryl group optionally substituted in the carbon skeleton by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a C_{3-7}-cycloalkyl, trifluoromethyl, phenyl or cyano group,

by a phenyl group which is substituted by a pyrrolidino, piperidino, piperazino, morpholino or thiomorpholino group, while the nitrogen atom in the 4 position of the piperazino

group may be substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, C_{1-8}-alkoxy-carbonyl, benzoyl, C_{1-3}-alkylaminocarbonyl, phenylaminocarbonyl or [sic],

by a phenylaminosulphonylphenyl or phenylsulphonyl-aminophenyl group,

by a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group or

by a hydroxycarbonyl, C_{1-3}-alkoxycarbonyl, phenyloxycarbonyl or heteroaryl-oxycarbonyl group,

a straight-chain C_{2-3}-alkyl group which is terminally substituted

by a hydroxy, C_{1-3}-alkoxy, phenoxy or phenyl-C_{1-3}-alkoxy group or

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, phenylcarbonylamino or N-(C_{1-3}-alkyl)phenylcarbonylamino group,

or R^5 and R^6 together with the enclosed nitrogen atom denote a pyrrolidino, piperidino, piperazino, morpholino or

thiomorpholino group, while the nitrogen atom in the 4 position of the piperazino group may be substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl or phenylaminocarbonyl group,

while, unless otherwise specified, by the term heteroaryl group mentioned above is meant a 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl or [1,2,3]-thiadiazol-4-yl group and

all the abovementioned phenyl groups, heteroaryl groups, aromatic or heteroaromatic parts of molecules may additionally be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom, by a cyano group or by a straight-chain or branched C_{1-3}-alkyl or trifluoromethyl group,

and/or a hydrogen atom bonded to a nitrogen atom of a heteroaryl group or heteroaromatic part of a molecule may be replaced by a C_{1-3}-alkyl, phenyl or C_{1-3}-alkylcarbonyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

Particularly preferred compounds of the above general formula I are those wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl or trifluoromethyl group,

R^2, R^3, R^4, R^5 and R^7, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group,

R^6 denotes a straight-chain or branched C_{1-4}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a phenylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group,

a C_{1-4}-alkyl-carbonylamino or C_{1-4}-alkoxy-carbonyl-amino group,

a phenyl, biphenyl or phenyl-C_{1-3}-alkylphenyl group,

a straight-chain C_{1-3}-alkyl group which is terminally substituted

by a phenyl or biphenyl group which may be substituted in each case by a straight-chain or branched C_{1-4}-alkyl group, by a trifluoromethyl or hydroxy group,

by a 2-pyridyl, 3-pyridyl, 4-pyridyl or 1H-benzimidazol-2-yl group,

by a phenyl group which is substituted by a 1-pyrrolyl, 2-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl or [1,2,3]-thiadiazol-4-yl group, wherein the abovementioned heteroaromatic groups may be substituted in the carbon skeleton by a phenyl, C_{1-4}-alkyl or C_{3-7}-cycloalkyl group,

by a phenyl group which is substituted by a pyrrolidino or piperidino group,

by a phenylaminosulphonylphenyl or phenylsulphonyl-aminophenyl group,

by a 4-piperidinyl group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl, C_{1-3}-alkyl-carbonyl, benzoyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl,

phenylamino-carbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group or

by a hydroxycarbonyl or C_{1-3}-alkoxycarbonyl group,

a straight-chain C_{2-3}-alkyl group which is terminally substituted

by a hydroxy or C_{1-3}-alkoxy group or

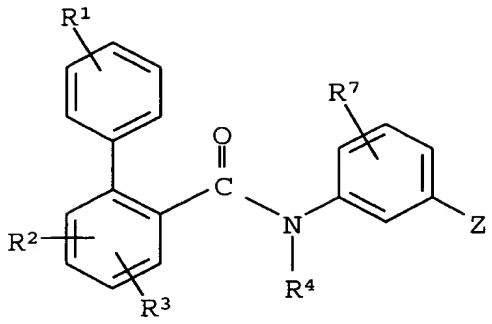
by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino group,

while all the abovementioned phenyl groups, heteroaryl groups, aromatic or heteroaromatic parts of molecules in the carbon skeleton may additionally be substituted by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-3}-alkyl group, by a cyano or a trifluoromethyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

According to the invention, the new compounds are obtained by methods known from the literature, e.g. by the following methods:

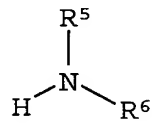
a. reacting a compound of general formula



, (II)

wherein
R^1 to R^4 and R^7 are as hereinbefore defined, and Z denotes a carboxy group or a reactive derivative of a carboxy group,

with an amine of general formula



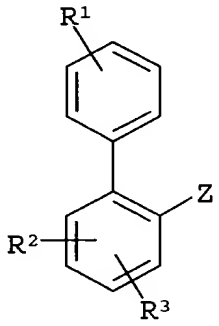
, (III)

wherein
R^5 and R^6 are as hereinbefore defined.

The reaction is expediently carried out with a corresponding halide or anhydride of general formula III in a solvent such as methylene chloride, chloroform, carbon tetrachloride, ether, tetrahydrofuran, dioxane, benzene, toluene, acetonitrile or sulpholane optionally in the presence of an inorganic or organic base at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C. However, it may also be carried out with the free acid, optionally in the presence of an acid-activating agent, e.g. propanephosphonic acid cycloanhydride or 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium-tetrafluoroborate (TBTU), or a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, hydrogen chloride, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus

pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexyl carbodiimide/N-hydroxysuccinimide or 1-hydroxy-benzotriazole, N,N'-carbonyldiimidazole or N,N'-thionyldiimidazole or triphenylphosphine/carbon tetrachloride, at temperatures between -20 and 200°C, but preferably at temperatures between -10 and 160°C.

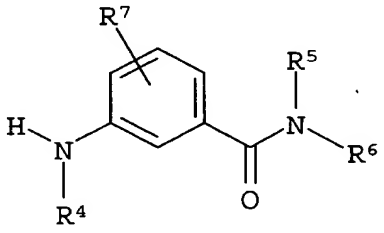
b. reacting a compound of general formula



, (IV)

wherein
R^1 to R^3 are as hereinbefore defined, and Z denotes a carboxy group or a reactive derivative of a carboxy group,

with an amine of general formula



, (V)

wherein
R^4 and R^7 are as hereinbefore defined.

The reaction may be carried out in accordance with the conditions mentioned above for method (a).

If according to the invention a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound of general formula I or

if a compound of general formula I is obtained which contains an amino, alkylamino or imino group, this may be converted by alkylation or reductive alkylation into a corresponding alkyl compound of general formula I or

if a compound of general formula I is obtained which contains a carboxy group, this may be converted by esterification into a corresponding ester of general formula I or

if a compound of general formula I is obtained which contains a carboxy or ester group, this may be converted by amidation into a corresponding amide of general formula I.

The subsequent acylation or sulphonylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with a corresponding acyl or sulphonyl derivative, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxybenzotriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent alkylation is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane with an alkylating agent such as a corresponding halide or sulphonic acid ester, e.g. with methyl iodide, ethyl bromide, dimethylsulphate or benzyl chloride, optionally in the presence of a tertiary organic base or in the presence of an inorganic base, expediently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 100°C.

The subsequent reductive alkylation is carried out with a corresponding carbonyl compound such as formaldehyde, acetaldehyde, propionaldehyde, acetone or butyraldehyde in the presence of a complex metal hydride such as sodium borohydride, lithium borohydride or sodium cyanoborohydride, expediently at a pH of 6-7 and at ambient temperature or in the presence of a hydrogenation catalyst, e.g. with hydrogen in the presence of palladium/charcoal, at a hydrogen pressure of 1 to 5 bar. However, the methylation is preferably carried out in the presence of formic acid as reducing agent at elevated temperatures, e.g. at temperatures between 60 and 120°C.

The subsequent esterification is optionally carried out in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane or most advantageously in a corresponding alcohol optionally in the presence of an acid such as hydrochloric acid or in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or

1-hydroxy-benztriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

The subsequent amidation is carried out by reacting a corresponding reactive carboxylic acid derivative with a corresponding amine, optionally in a solvent or mixture of solvents such as methylene chloride, dimethylformamide, benzene, toluene, chlorobenzene, tetrahydrofuran, benzene/tetrahydrofuran or dioxane, while the amine used may act as solvent at the same time, optionally in the presence of a tertiary organic base or in the presence of an inorganic base or with a corresponding carboxylic acid in the presence of a dehydrating agent, e.g. in the presence of isobutyl chloroformate, thionyl chloride, trimethylchlorosilane, sulphuric acid, methanesulphonic acid, p-toluenesulphonic acid, phosphorus trichloride, phosphorus pentoxide, O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium-tetrafluoroborate, N,N'-dicyclohexylcarbodiimide, N,N'-dicyclohexylcarbodiimide/N-hydroxysuccinimide or 1-hydroxy-benztriazole and optionally also in the presence of 4-dimethylamino-pyridine, N,N'-carbonyldiimidazole or triphenylphosphine/carbon tetrachloride, conveniently at temperatures between 0 and 150°C, preferably at temperatures between 0 and 80°C.

In the reactions described hereinbefore, any reactive groups present such as hydroxy, carboxy, amino, alkylamino or imino groups may be protected during the reaction by conventional protecting groups which are cleaved again after the reaction.

For example, a protecting group for a hydroxy group may be a trimethylsilyl, tert.butyl-dimethylsilyl, acetyl, benzoyl, methyl, ethyl, tert.butyl, trityl, benzyl or tetrahydropyranyl group,

a protecting group for a carboxyl group may be a trimethylsilyl, methyl, ethyl, tert.butyl, benzyl or tetrahydropyranyl group and

protecting groups for an amino, alkylamino or imino group may be a formyl, acetyl, trifluoroacetyl, ethoxycarbonyl, tert.butoxycarbonyl, benzyloxycarbonyl, benzyl, methoxybenzyl or 2,4-dimethoxybenzyl group and additionally, for the amino group, a phthalyl group.

Any protecting group used is optionally subsequently cleaved for example by hydrolysis in an aqueous solvent, e.g. in water, isopropanol/water, acetic acid/water, tetrahydrofuran/water or dioxane/water, in the presence of an acid such as trifluoroacetic acid, hydrochloric acid or sulphuric acid or in the presence of an alkali metal base such as sodium hydroxide or potassium hydroxide or aprotically, e.g. in the presence of iodotrimethylsilane, at temperatures between 0 and 120°C, preferably at temperatures between 10 and 100°C. However, a silyl group may also be cleaved using tetrabutylammonium fluoride as described hereinbefore.

However, a benzyl, methoxybenzyl or benzyloxycarbonyl group is cleaved, for example hydrogenolytically, e.g. with hydrogen in the presence of a catalyst such as palladium/charcoal in a suitable solvent such as methanol, ethanol, ethyl acetate or glacial acetic acid, optionally with the addition of an acid such as hydrochloric acid at temperatures between 0 and 100°C, but preferably at temperatures between 20 and 60°C, and at a hydrogen pressure of 1 to 7 bar, but preferably 3 to 5 bar. A 2,4-dimethoxybenzyl group, however, is preferably cleaved in trifluoroacetic acid in the presence of anisole.

A tert.butyl or tert.butyloxycarbonyl group is preferably cleaved by treating with an acid such as trifluoroacetic acid or hydrochloric acid or by treating with iodotrimethylsilane,

optionally using a solvent such as methylene chloride, dioxane, methanol or diethylether.

A trifluoroacetyl group is preferably cleaved by treating with an acid such as hydrochloric acid, optionally in the presence of a solvent such as acetic acid at temperatures between 50 and 120°C or by treating with sodium hydroxide solution, optionally in the presence of a solvent such as tetrahydrofuran at temperatures between 0 and 50°C.

A phthalyl group is preferably cleaved in the presence of hydrazine or a primary amine such as methylamine, ethylamine or n-butylamine in a solvent such as methanol, ethanol, isopropanol, toluene/water or dioxane at temperatures between 20 and 50°C.

Moreover, the compounds of general formula I obtained may be resolved into their enantiomers and/or diastereomers, as mentioned hereinbefore. Thus, for example, cis/trans mixtures may be resolved into their cis and trans isomers, and compounds with at least one optically active carbon atom may be separated into their enantiomers.

Thus, for example, the cis/trans mixtures obtained may be resolved by chromatography into the cis and trans isomers thereof, the compounds of general formula I obtained which occur as racemates may be separated by methods known *per se* (cf. Allinger N. L. and Eliel E. L. in "Topics in Stereochemistry", Vol. 6, Wiley Interscience, 1971) into their optical antipodes and compounds of general formula I with at least 2 asymmetric carbon atoms may be resolved into their diastereomers on the basis of their physical-chemical differences using methods known *per se*, e.g. by chromatography and/or fractional crystallisation, and, if these compounds are obtained in racemic form, they may subsequently be resolved into the enantiomers as mentioned above.

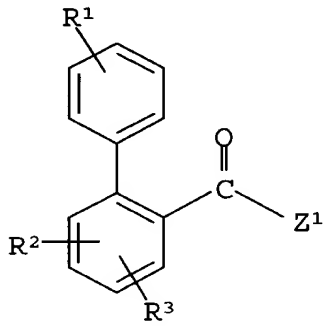
The enantiomers are preferably separated by column separation on chiral phases or by recrystallisation from an optically active solvent or by reacting with an optically active substance which forms salts or derivatives such as e.g. esters or amides with the racemic compound, particularly acids and the activated derivatives or alcohols thereof, and separating the diastereomeric mixture of salts or derivatives thus obtained, e.g. on the basis of their differences in solubility, whilst the free antipodes may be released from the pure diastereomeric salts or derivatives by the action of suitable agents. Optically active acids in common use are e.g. the D- and L-forms of tartaric acid or dibenzoyltartaric acid, di-o-tolyltartaric acid, malic acid, mandelic acid, camphorsulphonic acid, glutamic acid, aspartic acid or quinic acid. An optically active alcohol may be for example (+) or (-)-menthol and an optically active acyl group in amides, for example, may be a (+)-or (-)-menthyloxycarbonyl.

Furthermore, the compounds of formula I may be converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts with inorganic or organic acids. Acids which may be used for this purpose include for example hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid or maleic acid.

Moreover, if the new compounds of formula I thus obtained contain an acidic group such as a carboxy group, they may subsequently, if desired, be converted into the salts thereof with inorganic or organic bases, particularly for pharmaceutical use into the physiologically acceptable salts thereof. Suitable bases for this purpose include for example sodium hydroxide, potassium hydroxide, arginine, cyclohexylamine, ethanolamine, diethanolamine and triethanolamine.

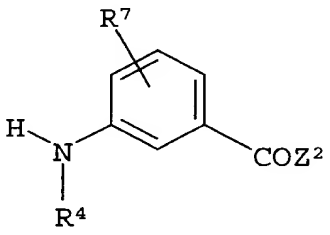
The compounds of general formulae II to V used as starting materials are either known from the literature or may be obtained by methods known from the literature or are described in the Examples.

A compound of general formula II is obtained, for example, by reacting a compound of general formula



, (VI)

wherein R^1 to R^3 are as hereinbefore defined and Z^1 denotes a carboxy group or a reactive derivative of a carboxy group, with an amine of general formula



, (VII)

wherein R^4 to R^7 are as hereinbefore defined and Z^2 denotes a protecting group for a carboxy group, and subsequently cleaving the protecting group.

The amines of general formula III wherein R^6 denotes a heteroaryl-aryl group or a heteroaryl-aryl-C_{1-6}-alkyl group, may be prepared, for example, by synthesising the heteroaromatic ring from suitably substituted aryl or aryl-C_{1-6}-alkyl educts, possibly by reactions of condensation with suitable dicarbonyl compounds.

The biphenyl-2-carboxylic acids according to general formula IV are known from the literature or may be prepared by methods known from the literature from corresponding biphenyl educts.

The 3-amino-benzoic acid amides according to general formula VI are also known from the literature or may easily be prepared from optionally substituted 3-aminobenzoic acids by reacting with the corresponding amines.

As already mentioned hereinbefore, the compounds of general formula I and the physiologically acceptable salts thereof have valuable pharmacological properties. In particular, they are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP) and are therefore suitable for lowering the plasma levels of the atherogenic lipoproteins.

For example, the compounds according to the invention were investigated for their biological effects as follows:

Inhibitors of MTP were identified by a cell-free MTP activity test. Solubilised liver microsomes from various species (e.g. rat, pig) can be used as the MTP source. To prepare the donor and acceptor vesicles, lipids dissolved in organic solvents were mixed in a suitable ratio and applied to the wall of glass container in a thin layer by blowing the solvent in a nitrogen current. The solution used to prepare donor vesicles contained 400 μM of phosphatidyl choline, 75 μM of cardiolipin and 10 μM of [^{14}C]-triolein (68.8 μCi/mg). To prepare the acceptor vesicles, a solution of 1.2 mM of phosphatidyl choline, 5 μM of triolein and 15 μM of [^{3}H]-dipalmitoyl-phosphatidyl choline (108 mCi/mg) was used. Vesicles are produced by wetting the dried lipids with test buffer and subsequently treating with ultrasound. Vesicle populations of uniform size were obtained by gel filtration of the ultrasound-treated lipids. The MTP activity test contains donor vesicles, acceptor vesicles as well as the MTP source in test buffer. Substances were added from concentrated DMSO-

containing stock solutions, the final concentration of DMSO in the test was 0.1%. The reaction was started by the addition of MTP. After a corresponding incubation time the transfer process was stopped by the addition of 500 µl of a SOURCE 30Q anion exchanger suspension (Pharmacia Biotech). The mixture was shaken for 5 minutes and the donor vesicles bound to the anion exchanger material were separated off by centrifuging. The radioactivity of [^{3}H] and [^{14}C] in the supernatant was determined by liquid scintillation measurement and from this the recovery of the acceptor vesicles and the triglyceride transfer speed was calculated.

In view of the abovementioned biological properties the compounds of general formula I and the physiologically acceptable salts thereof are particularly suitable for lowering the plasma concentration of atherogenic apolipoprotein B (apoB)-containing lipoproteins such as chylomicrons and/or very low density lipoproteins (VLDL) as well as the residues thereof such as low density lipoproteins (LDL) and/or lipoprotein(a) (Lp(a)), for treating hyperlipidaemias, for preventing and treating atherosclerosis and the clinical sequelae thereof, and for preventing and treating related disorders such as diabetes mellitus, adiposity and pancreatitis, oral administration being preferred.

The daily dose needed to achieve such an effect is between 0.5 and 500 mg, expediently between 1 and 350 mg, but preferably between 5 and 200 mg, in adults.

For this purpose, the compounds of formula I prepared according to the invention, optionally combined with other active substances such as other lipid-lowering agents, for example HMG-CoA-reductase-inhibitors, cholesterol biosynthesis inhibitors such as squalene synthase inhibitors and squalene cyclase inhibitors, bile acid-binding resins, fibrates, cholesterol resorption inhibitors, niacin, probucol, CETP

inhibitors and ACAT inhibitors together with one or more inert conventional carriers and/or diluents, e.g. with corn starch, lactose, glucose, microcrystalline cellulose, magnesium stearate, polyvinylpyrrolidone, citric acid, tartaric acid, water, water/ethanol, water/glycerol, water/sorbitol, water/polyethyleneglycol, propylene glycol, stearyl alcohol, carboxymethylcellulose or fatty substances such as hard fat or suitable mixtures thereof in conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The Examples which follow are intended to illustrate the invention in more detail:

Example 1

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid amide

a. 4-(3-methyl-5-phenyl-pyrazol-1-yl)-benzonitrile

A solution of 20.0 g (0.118 mol) of 4-cyanophenylhydrazine and 19.1 g (0.118 mol) of benzoylacetone in 600 ml methanol is combined with 16.7 ml of triethylamine and stirred for two days. The solvent is distilled off, the residue is distributed in dichloromethane/water and the combined organic extracts are dried. The residue is chromatographed on silica gel, eluting with dichloromethane.

Yield: 22.2 g (73% of theory),

R_f value: 0.9 (silica gel; dichloromethane/methanol= 19:1)

$C_{17}H_{13}N_3$ (259.31)

Mass spectrum : $(M+H)^+$ = 260

b. 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine

22.2 g (0.086 mol) of 4-(3-methyl-5-phenyl-pyrazol-1-yl)-benzonitrile are dissolved in 660 ml of methanolic ammonia and after the addition of Raney nickel hydrogenated at ambient temperature with hydrogen. The catalyst is filtered off and the solution is evaporated down. The residue is chromatographed on silica gel, eluting with dichloromethane/methanol = 4:1.

Yield: 22 g (97 % of theory),

R_f value: 0.2 (silica gel; dichloromethane/methanol= 9:1)

$C_{17}H_{17}N_3$ (263.35)

Mass spectrum : $(M+H)^+$ = 264

M^+ = 263

c. ethyl 3-(4'-methylbiphenyl-2-carbonylamino)-benzoate

1.6 g (9.9 mmol) of ethyl 3-aminobenzoate are placed in 80 ml of tetrahydrofuran and 2.8 mol (20 mmol) of triethylamine, a solution of 2.3 g (9.9 mmol) of 4'-methylbiphenyl-2-carboxylic acid chloride is added dropwise and the mixture is stirred for

1 more hour. The solvent is distilled off, the residue is distributed in ethyl acetate/water, the combined organic extracts are dried and evaporated down.
Yield: 3.5 g (98 % of theory),
R_f value: 0.7 (silica gel; dichloromethane/methanol= 19:1)

d. 3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid
3.5 g (9.7 mmol) of ethyl 4'-methylbiphenyl-2-carbonylamino)-benzoate are stirred in 100 ml methanol and 15 ml of 2 molar sodium hydroxide solution for 1 hour at 50°C. The solvent is distilled off, the residue is combined with water and acidified with 2 molar hydrochloric acid. Precipitated product is suction filtered.
Yield: 3.2 g (99% of theory),
R_f value: 0.2 (silica gel; dichloromethane/methanol= 19:1)

e. 3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid chloride
490 mg (1.5 mmol) of 4'-methylbiphenyl-2-carbonylamino)-benzoic acid are stirred in 5 ml thionyl chloride with the addition of 3 drops of dimethylformamide for 1 hour. Then the mixture is evaporated down and the residue is further reacted directly.
Yield: 518 mg (100% of theory).

f. N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid amide
A mixture of 518 mg (1.5 mmol) of 3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid chloride, 390 mg (1.5 mmol) of 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine and 0.7 ml (5 mmol) of triethylamine are stirred in 20 ml tetrahydrofuran for 1 hour. The solvent is distilled off and the residue chromatographed on silica gel, eluting with dichloromethane/ethanol 0-4 %.
Yield: 340 mg (40% of theory),
R_f value: 0.7 (silica gel; dichloromethane/ethanol = 9:1)
$C_{38}H_{32}N_4O_2$ (576.70)
Mass spectrum : $(M+H)^+$ = 577

$(M-H)^-$ = 575
$(M+Na)^+$ = 599

Example 2

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid chloride and 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 47 % of theory,

R_f value: 0.5 (silica gel; dichloromethane/ethanol = 19:1)

$C_{38}H_{29}F_3N_4O_2$ (630.67)

Mass spectrum : $(M+H)^+$ = 631
$(M-H)^-$ = 629
$(M+Na)^+$ = 653

Example 3

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(biphenyl-2-carbonylamino)-benzoic acid chloride and 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 54 % of theory,

R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)

$C_{37}H_{30}N_4O_2$ (562.67)

Mass spectrum : $(M+H)^+$ = 563
$(M-H)^-$ = 561
$(M+Na)^+$ = 585

Example 4

N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-fluorobiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(4'-fluorobiphenyl-2-carbonylamino)-benzoic acid chloride and 4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethylamine in tetrahydrofuran with the addition of triethylamine.

Yield: 52 % of theory,

R_f value: 0.2 (silica gel; dichloromethane/ethanol = 50:1)

$C_{37}H_{29}FN_4O_2$ (580.66)

Mass spectrum : $(M-H)^-$ = 579

$(M+Na)^+$ = 603

Example 5

N-[4-(N-methyl-N-phenylaminocarbonyl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid chloride and 4-amino-N-methyl-N-phenyl-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.

Yield: 37 % of theory,

R_f value: 0.5 (silica gel; dichloromethane/ethanol = 19:1)

$C_{36}H_{28}F_3N_3O_3$ (607.64)

Mass spectrum : $(M+H)^+$ = 608

$(M-H)^-$ = 606

$(M+Na)^+$ = 630

Example 6

N-[4-(N-methyl-N-phenylaminocarbonyl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from 3-(biphenyl-2-carbonylamino)-benzoic acid chloride and 4-amino-N-methyl-N-phenyl-benzoic acid amide in tetrahydrofuran with the addition of triethylamine

Yield: 35 % of theory,
R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)
$C_{35}H_{29}N_3O_3$ (539.64)
Mass spectrum : $(M+H)^+$ = 540
$(M-H)^-$ = 538
$(M+Na)^+$ = 562

Example 7

N-(biphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

A solution of 0.3 g (0.8 mmol) of 3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid, 0.1 g (0.8 mmol) of 4-phenyl-benzylamine and 0.5 ml (4.6 mmol) of N-methylmorpholine in 25 ml of dichloromethane is combined with 0.9 ml (1.6 mmol) of propanephosphonic acid cycloanhydride (50 wt-% in ethyl acetate) at -10°C and stirred for 2 hours while cooling. The mixture is chromatographed on silica gel, eluting with a gradient from 100%-dichloromethane to dichloromethane/methanol/ammonia = 20:77.5:2.5.
Yield: 0.2 g (47 % of theory),
R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{25}F_3N_2O_2$ (550.58)
Mass spectrum : $(M-H)^-$ = 549

Example 8

N-(pyridine-3-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-picolylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 81 % of theory
R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)
$C_{27}H_{20}F_3N_3O_2$ (475.47)
Mass spectrum : $(M-H)^-$ = 474

Example 9

N-(2-phenylethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 2-phenylethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 60 % of theory
R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)
$C_{29}H_{23}F_3N_2O_2$ (488.51)
Mass spectrum : $(M-H)^-$ = 487

Example 10

N-(4-benzoylamino-phenylmethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-benzoylamino-phenylmethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 57 % of theory
R_f value: 0.56 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{27}N_3O_3$ (525.61)
Mass spectrum : $(M-H)^-$ = 524

Example 11

N-(2-acetylamino-ethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenylene-2-carbonylamino)-benzoic acid and N-(2-amino-ethyl)-acetamide in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 41 % of theory

R_f value: 0.45 (silica gel; dichloromethane/ethanol = 9:1)
$C_{25}H_{22}F_3N_3O_3$ (469.46)
Mass spectrum : $(M-H)^-$ = 468

Example 12

N-(4-benzoylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-benzoylamino-phenylmethylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 30 % of theory
R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)
$C_{35}H_{26}F_3N_3O_3$ (593.61)
Mass spectrum : $(M-H)^-$ = 592

Example 13

N-phenyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and aniline in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 59 % of theory
R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)
$C_{27}H_{19}F_3N_2O_2$ (460.46)
Mass spectrum : $(M-H)^-$ = 459
$(M+Na)^+$ = 483

Example 14

N-methyl-N-propyl-3-(4'-trifluoromethylbiphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N-methyl-propylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 44 % of theory
R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)
$C_{25}H_{23}F_3N_2O_2$ (440.47)
Mass spectrum : $(M-H)^-$ = 439

Example 15

N-(2-ethoxycarbonylethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and β-alanine ethyl ester in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 11 % of theory
R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)
$C_{26}H_{23}F_3N_2O_4$ (484.48)
Mass spectrum : $(M-H)^-$ = 483
$(M+Na)^+$ = 507

Example 16

N-tert.butoxycarbonylamino-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and tert.butyl hydrazinoformate in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 46 % of theory

R_f value: 0.58 (silica gel; dichloromethane/ethanol = 9:1)
$C_{26}H_{24}F_3N_3O_4$ (499.49)
Mass spectrum : $(M-H)^-$ = 498

Example 17

N-phenylamino-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and phenylhydrazine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 8 % of theory
R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)
$C_{27}H_{20}F_3N_3O_2$ (475.47)
Mass spectrum : $(M-H)^-$ = 474
$(M+Na)^+$ = 498

Example 18

N-(N-tert.butoxycarbonyl-piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N-tert.butoxy-carbonyl-piperidin-4-yl-methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 38 % of theory
R_f value: 0.68 (silica gel; dichloromethane/ethanol = 9:1)
$C_{32}H_{34}F_3N_3O_4$ (581.64)
Mass spectrum : $(M-H)^-$ = 580
$(M+Na)^+$ = 604

Example 19

N-phenylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 46 % of theory
R_f value: 0.68 (silica gel; dichloromethane/ethanol = 9:1)
$C_{28}H_{21}F_3N_2O_2$ (474.49)
Mass spectrum : $(M-H)^-$ = 473
$(M+Na)^+$ = 497

Example 20

N-(biphenyl-2-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 2-phenyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 65 % of theory
R_f value: 0.74 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{25}F_3N_2O_2$ (550.59)
Mass spectrum : $(M-H)^-$ = 549
$(M+Na)^+$ = 573

Example 21

N-propyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and propylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 33 % of theory

R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)
$C_{24}H_{21}F_3N_2O_2$ (426.44)
Mass spectrum : $(M-H)^-$ = 425
$(M+Na)^+$ = 449

Example 22

N-ethoxycarbonylmethyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and glycine ethyl ester hydrochloride in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 79 % of theory
R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)
$C_{25}H_{21}F_3N_2O_4$ (470.45)
Mass spectrum : $(M-H)^-$ = 469
$(M+Na)^+$ = 493

Example 23

N-dimethylamino-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N,N-dimethylhydrazine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 57 % of theory
R_f value: 0.85 (silica gel; dichloromethane/ethanol = 9:1)
$C_{23}H_{20}F_3N_3O_2$ (427.43)
Mass spectrum : $(M-H)^-$ = 426
$(M+H)^+$ = 428
$(M+Na)^+$ = 450

Example 24

N-phenylmethyl-N-methyl-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and N-methyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 95 % of theory
R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)
$C_{29}H_{23}F_3N_2O_2$ (488.51)
Mass spectrum : $(M-H)^-$ = 487
$(M+Na)^+$ = 511

Example 25

N-[4-(phenylmethyl)-phenyl]-3-(4-methylbiphenyl-2-carbonyl-amino)-benzoic acid amide

Prepared analogously to Example 1f from 4'-methylbiphenyl-2-carboxylic acid chloride and 3-amino-N-(4-benzyl-phenyl)-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.
Yield: 83 % of theory,
R_f value: 0.6 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{28}N_2O_2$ (496.61)
Mass spectrum : $(M-H)^-$ = 495

Example 26

N-(biphenyl-3-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 3-phenylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 58 % of theory

R_f value: 0.71 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{25}F_3N_2O_2$ (550.59)
Mass spectrum : $(M-H)^-$ = 549
$(M+Na)^+$ = 573

Example 27

N-[4-(1H-imidazol-2-yl)-phenylmethyl]-3-(biphenyl-2-carbonylamino)-benzoic acid amide-hydrochloride

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonyl-amino)-benzoic acid and 4-(1H-imidazol-2-yl)benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 96 % of theory
R_f value: 0.5 (silica gel; dichloromethane/ethanol = 95:5)
$C_{30}H_{24}N_4O_2$ x HCl (472.54/509.01)
Mass spectrum : $(M+H)^+$ = 473

Example 28

N-(biphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonyl-amino)-benzoic acid and 4-phenylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 88 % of theory
R_f value: 0.76 (silica gel; dichloromethane/ethanol = 95:5)
$C_{33}H_{26}N_2O_2$ (482.59)
Mass spectrum : $(M-H)^-$ = 481
$(M+H)^+$ = 483
$(M+Na)^+$ = 505

Example 29

N-(4'-hydroxybiphenyl-4-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-benzoic acid and 4-(4-hydroxyphenyl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 6 % of theory
R_f value: 0.88 (silica gel; dichloromethane/ethanol = 95:5)
$C_{33}H_{26}N_2O_3$ (498.59)
Mass spectrum : $(M-H)^-$ = 497
$(M+Cl)^-$ = 533/35 (chlorine isotopes)

Example 30

N-(piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide-trifluoroacetate

0.2 g (0.27 mmol) of N-(N-tert.butoxycarbonyl-piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide are stirred in 30 ml dichloromethane and 3 ml of trifluoroacetic acid for 17 hours at ambient temperature. Then the mixture is evaporated to dryness *in vacuo*.
Yield: 0.2 g (98 % of theory),
R_f value: 0.42 (silica gel; dichloromethane/ethanol = 9:1)
$C_{27}H_{26}F_3N_3O_2$ x CF_3COOH (481.52/595.55)
Mass spectrum : $(M+H)^+$ = 482

Example 31

N-[N-(N-methyl-N-phenylaminocarbonyl)-piperidin-4-yl-methyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1f from N-(piperidin-4-yl-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide-trifluoroacetate and N-methyl-N-phenyl-

carbamoylchloride in tetrahydrofuran with the addition of triethylamine.
Yield: 99 % of theory,
R_f value: 0.57 (silica gel; dichloromethane/ethanol = 9:1)
$C_{35}H_{33}F_3N_4O_3$ (614.67)
Mass spectrum : $(M-H)^-$ = 613

Example 32

N-[4-(3-methyl-5-tert.butyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide
Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(5-tert.-butyl-3-methyl-pyrazol-1-yl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 53 % of theory
R_f value: 0.5 (silica gel; dichloromethane/ethanol = 19:1)
$C_{36}H_{33}F_3N_4O_2$ (610.69)
Mass spectrum : $(M-H)^-$ = 609
$(M+H)^+$ = 611
$(M+Na)^+$ = 633

Example 33

N-methyl-N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-(4'-methylbiphenyl-2-carbonylamino)-benzoic acid amide
Prepared analogously to Example 1c from 4'-methylbiphenyl-2-carboxylic acid chloride and N-methyl-N-[4-(3-methyl-5-phenyl-pyrazol-1-yl)-phenylmethyl]-3-amino-benzoic acid amide in tetrahydrofuran with the addition of triethylamine.
Yield: 22 % of theory
R_f value: 0.6 (silica gel; dichloromethane/methanol= 9:1)
$C_{39}H_{34}N_4O_2$ (590.73)
Mass spectrum : $(M-H)^-$ = 589
$(M+H)^+$ = 591

Example 34

N-(pyridine-3-yl-methyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

3.2 mg (10 µmol) of 3-(biphenyl-2-carbonylamino)-benzoic acid are placed in 0.4 ml dimethylformamide and after the addition of 1.6 mg (15 µmol) of 3-picolylamine, 3.9 mg (12 µmol) of O-(benzo-triazol-1-yl)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TBTU) and 7 mg (50 µmol) of N-ethyl-diisopropylamine the mixture is stirred for 12 hours. The solution is evaporated down.

R_f value: 0.2 (silica gel; dichloromethane/ethanol = 19:1)

$C_{26}H_{21}N_3O_2$ (407.47)

Mass spectrum : $(M+H)^+$ = 408

Example 35

N-phenyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, aniline, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 19:1)

$C_{26}H_{20}N_2O_2$ (392.46)

Mass spectrum : $(M+Na)^+$ = 415

Example 36

N-tert.butyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonyl-amino)-benzoic acid, tert.butylamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.4 (silica gel; dichloromethane/ethanol = 19:1)

$C_{24}H_{24}N_2O_2$ (372.47)

Mass spectrum : $(M+Na)^+$ = 395

Example 37

N-hydroxyethyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, 2-aminoethanol, TBTU and N-ethyl-diisopropylamine in dimethylformamide.

R_f value: 0.2 (silica gel; dichloromethane/ethanol = 19:1)

$C_{22}H_{20}N_2O_3$ (360.41)

Mass spectrum : $(M+Na)^+$ = 383

Example 38

N-(2-dimethylamino-ethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, N,N-dimethylethylenediamine, TBTU and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 4:1)

$C_{24}H_{25}N_3O_2$ (387.48)

Mass spectrum : $(M+H)^+$ = 388

M^+ = 387

Example 39

N-(2-carboxy-ethyl)-3-(biphenyl-2-carbonylamino)-benzoic acid amide-sodium salt

Prepared analogously to Example 34 from 3-(biphenyl-2-carbonylamino)-benzoic acid, β-alanine, TBTU, sodium hydroxide solution and N-ethyldiisopropylamine in dimethylformamide.

R_f value: 0.15 (silica gel; dichloromethane/ethanol = 9:1)

$C_{23}H_{19}NaN_2O_4$ (410.41), free acid $C_{23}H_{20}N_2O_4$ (388.42)

Mass spectrum : $(M-H)^-$ = 387

Example 40

N-(4-[1,2,3]-thiadiazol-4-yl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-[1,2,3]-thiadiazol-4-yl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 18 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)

$C_{30}H_{21}F_3N_4O_2S$ (558.58)

Mass spectrum : $(M-H)^-$ = 557
$(M+H)^+$ = 559
$(M+Na)^+$ = 581

Example 41

N-(4-phenylaminosulphonyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-aminomethyl-N-phenyl-benzenesulphonamide in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 73 % of theory

R_f value: 0.68 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{26}F_3N_3O_4S$ (629.66)

Mass spectrum : $(M-H)^-$ = 628
$(M+H)^+$ = 630
$(M+Na)^+$ = 652

Example 42

N-(4-piperidin-1-yl-phenylmethyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-piperidin-1-yl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 47 % of theory

R_f value: 0.69 (silica gel; dichloromethane/ethanol = 9:1)

$C_{33}H_{30}F_3N_3O_2$ (557.61)

Mass spectrum : $(M-H)^-$ = 556

$(M+Na)^+$ = 580

Example 43

N-(4-phenylsulphonylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-phenylsulphonylamino-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 57 % of theory

R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)

$C_{34}H_{26}F_3N_3O_4S$ (629.66)

Mass spectrum : $(M-H)^-$ = 628

$(M+H)^+$ = 630

$(M+Na)^+$ = 652

Example 44

N-[4-(2-methyl-pyrrol-1-yl)-phenylmethyl]-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-

(2-methyl-pyrrol-1-yl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 22 % of theory
R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)
$C_{33}H_{26}F_3N_3O_2$ (553.58)
Mass spectrum : $(M-H)^-$ = 552
$(M+H)^+$ = 554
$(M+Na)^+$ = 576

Example 45

N-(2'-methylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(2-methylphenyl)benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 21 % of theory
R_f value: 0.72 (silica gel; dichloromethane/ethanol = 9:1)
$C_{35}H_{27}F_3N_2O_2$ (564.60)
Mass spectrum : $(M-H)^-$ = 563
$(M+Na)^+$ = 587

Example 46

N-(4-tert.butyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-tert.butyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 53 % of theory
R_f value: 0.69 (silica gel; dichloromethane/ethanol = 9:1)
$C_{32}H_{29}F_3N_2O_2$ (530.59)
Mass spectrum : $(M-H)^-$ = 529
$(M+Na)^+$ = 553

Example 47

N-(4-isopropyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-isopropylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 58 % of theory
R_f value: 0.67 (silica gel; dichloromethane/ethanol = 9:1)
$C_{31}H_{27}F_3N_2O_2$ (516.56)
Mass spectrum : $(M-H)^-$ = 515
$(M+Na)^+$ = 539

Example 48

N-(4-Bromophenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-bromobenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 51 % of theory
R_f value: 0.64 (silica gel; dichloromethane/ethanol = 9:1)
$C_{28}H_{20}BrF_3N_2O_2$ (553.38)
Mass spectrum : $(M-H)^-$ = 551/53 (bromine isotopes)
$(M+Na)^+$ = 575/77 (bromine isotopes)

Example 49

N-(4-trifluoromethyl-phenylmethyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-trifluoromethyl-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 48 % of theory
R_f value: 0.63 (silica gel; dichloromethane/ethanol = 9:1)
$C_{29}H_{20}F_6N_2O_2$ (542.48)
Mass spectrum : $(M-H)^-$ = 541
$(M+Na)^+$ = 565

Example 50

N-(4-acetylamino-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-acetylaminobenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 38 % of theory
R_f value: 0.60 (silica gel; dichloromethane/ethanol = 9:1)
$C_{30}H_{24}F_3N_3O_3$ (531.53)
Mass spectrum : $(M+Na)^+$ = 554

Example 51

N-(1H-benzimidazol-2-yl-methyl)-3-(4'-trifluoromethyl-biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 2-(aminomethyl)-benzimidazole in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 19 % of theory
R_f value: 0.58 (silica gel; dichloromethane/ethanol = 9:1)
$C_{29}H_{21}F_3N_4O_2$ (514.51)
Mass spectrum : $(M-H)^-$ = 513
$(M+H)^+$ = 515

Example 52

N-(4'-methylbiphenyl-4-methyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-(4'-methylphenyl)-benzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 21 % of theory

R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)

$C_{35}H_{27}F_3N_2O_2$ (564.61)

Mass spectrum : $(M-H)^-$ = 563

$(M+Na)^+$ = 587

Example 53

N-(4-methyl-phenylmethyl)-3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(4'-trifluoromethylbiphenyl-2-carbonylamino)-benzoic acid and 4-methylbenzylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.

Yield: 82 % of theory

R_f value: 0.75 (silica gel; dichloromethane/ethanol = 9:1)

$C_{29}H_{23}F_3N_2O_2$ (488.51)

Mass spectrum : $(M-H)^-$ = 487

$(M+Na)^+$ = 511

Example 54

N-(biphenyl-4-methyl)-2-methyl-5-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 1c from biphenyl-2-carboxylic acid chloride and N-(biphenyl-4-methyl)-2-methyl-5-amino-benzoic acid amide in tetrahydrofuran and triethylamine.

Yield: 92 % of theory

R_f value: 0.74 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{28}N_2O_2$ (496.61)
Mass spectrum : $(M-H)^-$ = 495
$(M+Na)^+$ = 519

Example 55

N-(biphenyl-4-methyl)-4-methyl-3-(biphenyl-2-carbonylamino)-benzoic acid amide

Prepared analogously to Example 7 from 3-(biphenyl-2-carbonylamino)-4-methyl-benzoic acid and biphenyl-4-methylamine in dichloromethane with the addition of propanephosphonic acid cycloanhydride and N-methylmorpholine.
Yield: 30 % of theory
R_f value: 0.73 (silica gel; dichloromethane/ethanol = 9:1)
$C_{34}H_{28}N_2O_2$ (496.61)
Mass spectrum : $(M-H)^-$ = 495

Example 56

Tablets containing 5 mg of active substance per tablet

Composition:

active substance	5.0 mg
lactose monohydrate	70.8 mg
microcrystalline cellulose	40.0 mg
sodium carboxymethylcellulose, insolubly crosslinked	3.0 mg
magnesium stearate	1.2 mg

Preparation:

The active substance is mixed for 15 minutes with lactose monohydrate, microcrystalline cellulose and sodium carboxymethylcellulose in a suitable diffusion mixer. Magnesium stearate is added and mixed with the other substances for another 3 minutes.

The finished mixture is compressed in a tablet press to form facetted flat round tablets.
Diameter of the tablet: 7 mm
Weight of the tablet: 120 mg

Example 57

Capsules containing 50 mg of active substance per capsule

Composition:

active substance	50.0 mg
lactose monohydrate	130.0 mg
corn starch	65.0 mg
highly dispersed silicon dioxide	2.5 mg
magnesium stearate	2.5 mg

Preparation:

A starch paste is prepared by allowing some of the corn starch to swell in a suitable amount of hot water. The paste is then left to cool to room temperature.
The active substance is premixed for 15 minutes in a suitable mixer with lactose monohydrate and corn starch. The starch paste is added and the mixture is mixed with sufficient water to produce a moist homogeneous mass. The moist mass is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Highly dispersed silica is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium stearate is added and mixing is continued for another 3 minutes.

The finished mixture is packed into empty size 1 hard gelatine capsule shells using a capsule filling machine.

The finished mixture is packed into empty size 1 hard gelatine capsule shells using a capsule filling machine.

Example 58

Tablets containing 200 mg of active substance per tablet

Composition:

active substance	200.0 mg
lactose-monohydrate	167.0 mg
microcrystalline cellulose	80.0 mg
hydroxypropyl-methylcellulose, type 2910	10.0 mg
poly-1-vinyl-2-pyrrolidone, insolubly crosslinked	20.0 mg
magnesium stearate	3.0 mg

Preparation:
HPMC is dispersed in hot water. After cooling, the mixture yields a clear solution.

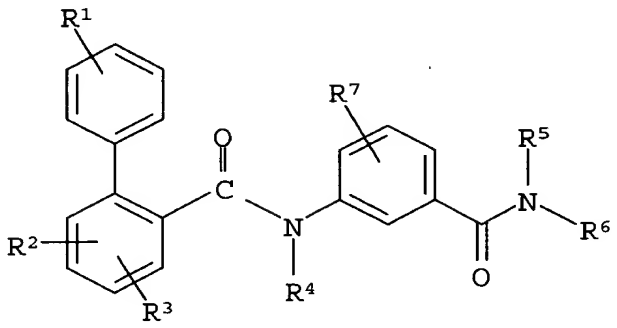
The active substance is premixed in a suitable mixer for 5 minutes with lactose monohydrate and microcrystalline cellulose. The HPMC solution is added and the mixing is continued until a homogeneous moist composition is obtained. The moist composition is passed through a screen with a mesh size of 1.6 mm. The screened granules are dried on racks at about 55°C for 12 hours.

The dried granules are then passed through screens with mesh sizes of 1.2 and 0.8 mm. Poly-1-vinyl-2-pyrrolidone is mixed with the granules in a suitable mixer for 3 minutes. Then magnesium stearate is added and mixing is continued for another 3 minutes.

The finished mixture is compressed in a tablet press to form oblong tablets (16.2 x 7.9 mm).
Weight of a tablet: 480 mg

Patent Claims

1. Biphenylcarboxylic acid amides of general formula



, (I)

wherein

R^1, R^2 and R^3, which may be identical or different, in each case denote a hydrogen, fluorine, chlorine or bromine atom, a straight-chain or branched C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms, a hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino- or di-(C_{1-3}-alkyl)-amino group,

R^4 denotes a hydrogen atom or a C_{1-3}-alkyl group,

R^5 denotes a hydrogen atom or a straight-chain or branched C_{1-6}-alkyl group and

R^6 denotes a straight-chain or branched C_{1-6}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-amino group, wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen

or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-(C_{1-3}-alkyl)-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

an arylamino, N-(C_{1-3}-alkyl)-arylamino, heteroarylamino, N-(C_{1-3}-alkyl)-heteroarylamino, C_{1-7}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-7}-alkyl-carbonylamino, arylcarbonylamino, heteroarylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino, N-(C_{1-3}-alkyl)-heteroarylcarbonylamino, C_{1-8}-alkoxy-carbonyl-amino or N-(C_{1-3}-alkyl)-(C_{1-8}-alkoxy)-carbonylamino group,

an aryl or aryl-C_{1-3}-alkyl-aryl group,

a heteroaryl group,

an aryl group substituted by a heteroaryl group,

a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-(C_{1-3}-alkyl)-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

a phenylcarbonylamino-aryl, phenylaminocarbonyl-aryl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-aryl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-aryl group,

a straight-chain or branched C_{1-6}-alkyl group which is terminally substituted

by an aryl or heteroaryl group,

by an aryl group which is fused to a heteroaryl group via two adjacent carbon atoms,

by a heteroaryl group which is fused to an aryl or heteroaryl group via two adjacent carbon atoms,

by an aryl group which is substituted by an aryl or heteroaryl group, by a 4 to 7 membered cycloalkyleneimino group, by a phenylaminosulphonyl or phenylsulphonylamino group,

by a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of a 6- or 7-membered cycloalkyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-8}-alkyl-carbonyl, C_{1-8}-alkoxycarbonyl, benzoyl, phenyl-(C_{1-3}-alkyl-carbonyl), C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-aryl, phenylaminocarbonyl-aryl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-aryl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-aryl group or

by a hydroxycarbonyl, C_{1-3}-alkoxycarbonyl, C_{3-7}-cycloalkyloxycarbonyl, aryloxycarbonyl, heteroaryloxycarbonyl, aryl-C_{1-3}-alkoxycarbonyl or heteroaryl-C_{1-3}-alkoxycarbonyl group,

a straight-chain or branched C_{2-6}-alkyl group which is terminally substituted

by a hydroxy, C_{1-3}-alkoxy, aryloxy, heteroaryloxy-aryl-C_{1-3}-alkoxy or heteroaryl-C_{1-3}-alkoxy group,

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkylcarbonylamino, arylcarbonylamino, heteroarylcarbonylamino, N-(C_{1-3}-alkyl)-arylcarbonylamino or N-(C_{1-3}-alkyl)-heteroarylcarbonylamino group,

or R^5 and R^6 together with the enclosed nitrogen atom denote a 4- to 7-membered cycloalkyleneimino group,

R^7 denotes a hydrogen, chlorine, bromine or iodine atom, a C_{1-3}-alkyl or C_{1-3}-alkoxy group,

wherein by the term aryl group used above is meant a phenyl, 1-naphthyl or 2-naphthyl group,

by the term heteroaryl group used above is meant a 5-membered heteroaromatic ring linked via a nitrogen or carbon atom, which contains

an imino group, an oxygen or sulphur atom,

an imino group and an oxygen, sulphur or nitrogen atom,

an imino group and two nitrogen atoms or

two imino groups and an oxygen or sulphur atom,

or a 6-membered heteroaromatic ring linked via a carbon atom which contains one or two nitrogen atoms,

and wherein a 1,4-butadienylene group may be attached both to the abovementioned 5-membered and also to the 6-membered heteroaromatic rings in each case via two adjacent carbon atoms and the bicyclic heteroaromatic rings thus formed may also be bonded via a carbon atom of the 1,4- butadienylene group,

a hydrogen atom bonded to a nitrogen atom of the abovementioned 5-membered monocyclic or fused heteroaryl groups may be replaced by a C_{1-3}-alkyl, phenyl, phenyl-C_{1-3}-alkyl, C_{1-3}-alkylcarbonyl, phenylcarbonyl or phenyl-C_{1-3}-alkylcarbonyl group,

all the abovementioned phenyl, aryl and heteroaryl groups as well as aromatic or heteroaromatic parts of molecules in the carbon skeleton may be monosubstituted by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a C_{3-7}-cycloalkyl, trifluoromethyl, phenyl, hydroxy, C_{1-3}-alkoxy, trifluoromethoxy, amino, C_{1-3}-alkylamino, acetylamino, propionylamino, benzoylamino, N-(C_{1-3}-alkyl)-benzoylamino, acetyl, propionyl, benzoyl, C_{1-3}-alkoxy-carbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or cyano group or, with the exception of 5-membered heteroaryl groups or heteroaromatic parts of molecules containing more than two heteroatoms, may also be disubstituted by the abovementioned substituents, while the substituents may be identical or different,

in all the abovementioned 4- 7-membered cycloalkyleneimino groups the cycloalkylene moiety may be fused to a phenyl ring or

one or two hydrogen atoms in each case may be replaced by a C_{1-3}-alkyl group and/or

in each case the methylene group in position 4 of a 6- or 7-membered cycloalkyleneimino group may be substituted by a hydroxycarbonyl, C_{1-6}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-C_{1-3}-alkylamino or N-(C_{1-3}-alkyl)-phenyl-C_{1-3}-alkylamino group or

may be replaced by an oxygen or sulphur atom, by a sulphinyl or sulphonyl group or by an imino group optionally substituted

by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, phenyl-C_{1-3}-alkyl-carbonyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

additionally any carboxy, amino or imino group present in the abovementioned groups may be substituted by a group which can be cleaved *in vivo*, and may thus occur in the form of a prodrug group,

and by a group which can be cleaved *in vivo* from an imino or amino group is meant, for example, a hydroxy group, an acyl group such as the benzoyl or pyridinoyl group or a C_{1-16}-alkanoyl group such as the formyl, acetyl, propionyl, butanoyl, pentanoyl or hexanoyl group, an allyloxycarbonyl group, a C_{1-16}-alkoxycarbonyl group such as the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, isopropoxycarbonyl, butoxycarbonyl, tert.butoxycarbonyl, pentoxycarbonyl, hexyloxycarbonyl, octyloxycarbonyl, nonyloxycarbonyl, decyloxycarbonyl, undecyloxycarbonyl, dodecyloxycarbonyl or hexadecyloxycarbonyl group, a phenyl-C_{1-6}-alkoxycarbonyl group such as the benzyloxycarbonyl, phenylethoxycarbonyl or phenylpropoxycarbonyl group, a C_{1-3}-alkylsulphonyl-C_{2-4}-alkoxycarbonyl, C_{1-3}-alkoxy-C_{2-4}-alkoxy-C_{2-4}-alkoxycarbonyl or R_eCO-O-(R_fCR_g)-O-CO group wherein

R_e denotes a C_{1-8}-alkyl, C_{5-7}-cycloalkyl, phenyl or phenyl-C_{1-3}-alkyl group,

R_f denotes a hydrogen atom, a C_{1-3}-alkyl, C_{5-7}-cycloalkyl or phenyl group and

R_g denotes a hydrogen atom, a C_{1-3}-alkyl or R_eCO-O-(R_fCR_g)-O group wherein R_e to R_g are as hereinbefore defined,

wherein the abovementioned ester groups may also be used as a group which can be converted *in vivo* into a carboxy group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

2. Compounds of formula I according to claim 1, wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom or a C_{1-3}-alkyl group wherein the hydrogen atoms may be wholly or partially replaced by fluorine atoms,

R^2, R^3, R^4, R^5 and R^7, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group,

R^6 denotes a straight-chain or branched C_{1-4}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a C_{3-7}-cycloalkylamino or N-(C_{1-3}-alkyl)-C_{3-7}-cycloalkyl-amino group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, C_{1-8}-alkoxy-carbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenyl-aminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

a phenylamino, 1-naphthylamino or 2-naphthylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group,

a C_{1-4}-alkyl-carbonylamino, phenylcarbonylamino or C_{1-8}-alkoxy-carbonylamino group,

a phenyl, biphenyl, 1-naphthyl, 2-naphthyl or phenyl-C_{1-3}-alkylphenyl group which may be substituted in the

aromatic moieties in each case by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a trifluoromethyl, hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, acetylamino, benzoylamino, acetyl, propionyl, benzoyl, C_{1-3}-alkoxy-carbonyl, amino-carbonyl, C_{1-3}-alkylamino-carbonyl or cyano group,

a heteroaryl group or a heteroaryl-phenyl group,

a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group,

a straight-chain C_{1-3}-alkyl group which is terminally substituted

by a phenyl, biphenyl, 1-naphthyl or 2-naphthyl group optionally substituted by a fluorine, chlorine, bromine or iodine atom, a straight-chain or branched C_{1-4}-alkyl group, a trifluoromethyl, hydroxy, C_{1-3}-alkoxy, amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, acetylamino, benzoylamino, acetyl, propionyl, benzoyl, C_{1-3}-alkoxycarbonyl, aminocarbonyl, C_{1-3}-alkylamino-carbonyl or cyano group,

by a heteroaryl group optionally substituted in the carbon skeleton by a fluorine, chlorine, bromine or iodine atom, by

a straight-chain or branched C_{1-4}-alkyl or C_{1-3}-alkoxy group, by a trifluoromethyl, phenyl or cyano group,

by an indolyl, benzimidazolyl, quinolinyl, isoquinolinyl, quinoxalinyl or quinazolinyl group bonded via a carbon atom or, in the case of the first two groups, via a nitrogen atom,

by a phenyl group which is substituted by a heteroaryl group optionally substituted in the carbon skeleton by a fluorine, chlorine, bromine or iodine atom, by a straight-chain or branched C_{1-4}-alkyl group, by a C_{3-7}-cycloalkyl, trifluoromethyl, phenyl or cyano group,

by a phenyl group which is substituted by a pyrrolidino, piperidino, piperazino, morpholino or thiomorpholino group, while the nitrogen atom in the 4 position of the piperazino group may be substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, C_{1-8}-alkoxy-carbonyl, benzoyl, C_{1-3}-alkylaminocarbonyl, phenylaminocarbonyl or [sic],

by a phenylaminosulphonylphenyl or phenylsulphonyl-aminophenyl group,

by a C_{3-7}-cycloalkyl group, wherein

in each case the methylene group in the 4 position of the cyclohexyl group may be replaced by an oxygen or sulphur atom or by an imino group optionally substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkyl-carbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylaminocarbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group or

by a hydroxycarbonyl, C_{1-3}-alkoxycarbonyl, phenyloxycarbonyl or heteroaryl-oxycarbonyl group,

a straight-chain C_{2-3}-alkyl group which is terminally substituted

by a hydroxy, C_{1-3}-alkoxy, phenoxy or phenyl-C_{1-3}-alkoxy group or

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino, N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino, phenylcarbonylamino or N-(C_{1-3}-alkyl)phenylcarbonylamino group,

or R^5 and R^6 together with the enclosed nitrogen atom denote a pyrrolidino, piperidino, piperazino, morpholino or thiomorpholino group, while the nitrogen atom in the 4 position of the piperazino group may be substituted by a C_{1-3}-alkyl, phenyl, C_{1-3}-alkylcarbonyl, benzoyl, C_{1-3}-alkyl-aminocarbonyl or phenylaminocarbonyl group,

while, unless otherwise specified, by the term heteroaryl group used above is meant a 2-pyridyl, 3-pyridyl, 4-pyridyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furyl, 3-furyl, 2-thienyl, 3-thienyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl or [1,2,3]-thiadiazol-4-yl group and

all the abovementioned phenyl groups, heteroaryl groups, aromatic or heteroaromatic parts of molecules may additionally be substituted in the carbon skeleton by a fluorine, chlorine or bromine atom, by a cyano group or by a straight-chain or branched C_{1-3}-alkyl or trifluoromethyl group,

and/or a hydrogen atom bonded to a nitrogen atom of a heteroaryl group or heteroaromatic part of a molecule may be replaced by a C_{1-3}-alkyl, phenyl or C_{1-3}-alkylcarbonyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

3. Compounds of formula I according to claim 1, wherein

R^1 denotes a hydrogen, fluorine, chlorine or bromine atom, a C_{1-3}-alkyl or trifluoromethyl group,

R^2, R^3, R^4, R^5 and R^7, which may be identical or different, in each case denote a hydrogen atom or a C_{1-3}-alkyl group,

R^6 denotes a straight-chain or branched C_{1-4}-alkyl group,

an amino, C_{1-3}-alkylamino or di-(C_{1-3}-alkyl)-amino group,

a phenylamino group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl group,

a C_{1-4}-alkyl-carbonylamino or C_{1-4}-alkoxy-carbonyl-amino group,

a phenyl, biphenyl or phenyl-C_{1-3}-alkylphenyl group,

a straight-chain C_{1-3}-alkyl group which is terminally substituted

by a phenyl or biphenyl group which may be substituted in each case by a straight-chain or branched C_{1-4}-alkyl group, by a trifluoromethyl or hydroxy group,

by a 2-pyridyl, 3-pyridyl, 4-pyridyl or 1H-benzimidazol-2-yl group,

by a phenyl group which is substituted by a 1-pyrrolyl, 2-pyrrolyl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrazolyl, 3-pyrazolyl, 4-pyrazolyl, 2-thiazolyl, 4-thiazolyl, 5-thiazolyl or [1,2,3]-thiadiazol-4-yl group, wherein the abovementioned heteroaromatic groups may be substituted in the carbon skeleton by a phenyl, C_{1-4}-alkyl or C_{3-7}-cycloalkyl group,

by a phenyl group which is substituted by a pyrrolidino or piperidino group,

by a phenylaminosulphonylphenyl or phenylsulphonyl-aminophenyl group,

by a 4-piperidinyl group optionally substituted at the nitrogen atom by a C_{1-3}-alkyl, C_{1-3}-alkyl-carbonyl, benzoyl, C_{1-3}-alkylaminocarbonyl, di-(C_{1-3}-alkyl)-aminocarbonyl, phenylamino-carbonyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl group,

by a phenylcarbonylamino-phenyl, phenylaminocarbonyl-phenyl, N-(C_{1-3}-alkyl)-phenylcarbonylamino-phenyl or N-(C_{1-3}-alkyl)-phenylaminocarbonyl-phenyl group or

by a hydroxycarbonyl or C_{1-3}-alkoxycarbonyl group,

a straight-chain C_{2-3}-alkyl group which is terminally substituted

by a hydroxy or C_{1-3}-alkoxy group or

by an amino, C_{1-3}-alkylamino, di-(C_{1-3}-alkyl)-amino, C_{1-3}-alkyl-carbonylamino or N-(C_{1-3}-alkyl)-C_{1-3}-alkyl-carbonylamino group,

while all the abovementioned phenyl groups, heteroaryl groups, aromatic or heteroaromatic parts of molecules in the carbon

skeleton may additionally be substituted by a fluorine, chlorine or bromine atom, by a straight-chain or branched C_{1-3}-alkyl group, by a cyano or a trifluoromethyl group,

the tautomers, the diastereomers, the enantiomers, the mixtures thereof and the salts thereof.

4. Physiologically acceptable salts of the compounds according to claims 1 to 3.

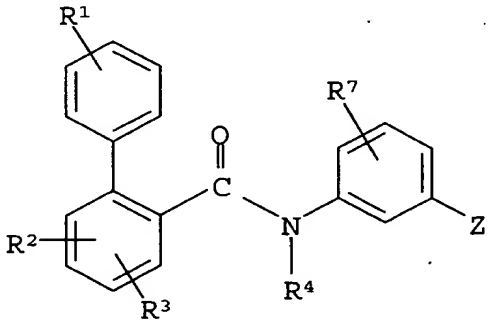
5. Medicaments, containing a compound according to at least one of claims 1 to 3 or a salt according to claim 4 optionally together with one or more inert carriers and/or diluents.

6. Use of a compound according to at least one of claims 1 to 3 or a salt according to claim 4 for the preparation of a medicament having a lowering effect on the plasma levels of atherogenic lipoproteins.

7. Process for preparing a medicament according to claim 5, characterised in that a compound according to at least one of claims 1 to 3 or a salt according to claim 3 is incorporated in one or more inert carriers and/or diluents by a non-chemical method.

8. Process for preparing the compounds according to claims 1 to 4, characterised in that

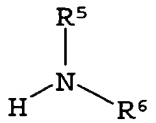
a. a compound of general formula



, (II)

wherein
R^1 to R^4 and R^7 are defined as in claims 1 to 3, and Z denotes a carboxy group or a reactive derivative of a carboxy group,

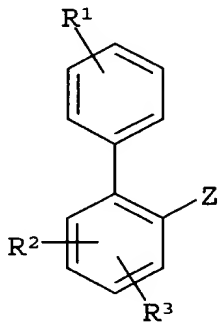
is reacted with an amine of general formula



, (III)

wherein
R^5 and R^6 are defined as in claims 1 to 3, or

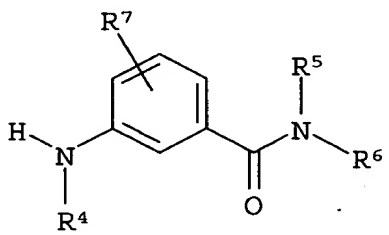
b. a compound of general formula



, (IV)

wherein
R^1 to R^3 are defined as in claims 1 to 3, and Z denotes a carboxy group or a reactive derivative of a carboxy group,

is reacted with an amine of general formula



, (V)

wherein
R^4 and R^7 are defined as in claims 1 to 3, and

subsequently, if desired, a compound of general formula I thus obtained which contains an amino, alkylamino or imino group, is converted by acylation or sulphonylation into a corresponding acyl or sulphonyl compound and/or

a compound of general formula I thus obtained which contains an amino, alkylamino or imino group is converted by alkylation or reductive alkylation into a corresponding alkyl compound and/or

a compound of general formula I thus obtained which contains a carboxy group is converted by esterification into a corresponding ester and/or

a compound of general formula I thus obtained which contains a carboxy or ester group is converted by amidation into a corresponding amide and/or

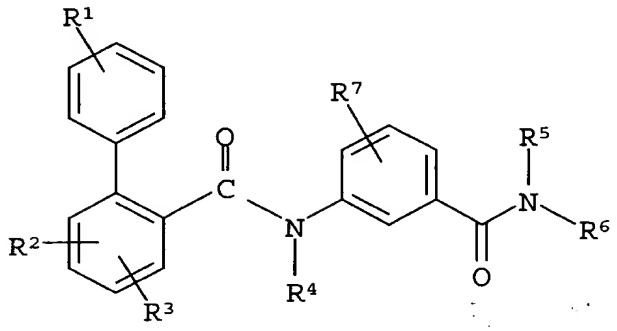
if necessary, any protecting group used during the reactions to protect reactive groups is cleaved and/or

a compound of general formula I thus obtained is resolved into the stereoisomers thereof and/or

a compound of general formula I thus obtained is converted into the salts thereof, particularly for pharmaceutical use into the physiologically acceptable salts thereof with an inorganic or organic acid or base.

Abstract

The present invention relates to substituted piperazine derivatives of general formula



, (I)

wherein
R^1 to R^7 are defined as in claim 1, the isomers and salts thereof, particularly the physiologically acceptable salts thereof, which are valuable inhibitors of the microsomal triglyceride-transfer protein (MTP), medicaments containing these compounds and their use, as well as the preparation thereof.